XNEOr: Development and Evaluation of an Expert System to Improve the Quality and Cost of Decision-Making in Neuro-Oncology

Bernard L. Maria, M.D., Ferose A. Lambay, Douglas Dankel II, Ph.D.,

Sharma Chakravarthy, Ph.D., Suleyman Tufekci, Ph.D., Robert Marcus, M.D.,

Amos Kedar, M.D., University of Florida, Gainesville, FL.

The treatment of brain tumors requires a large team of medical experts. However, the process of medical decision-making for these patients is hampered by the frequent inaccessibility of the experts because of conflicting scheduling, inconsistencies in the management of different patients, and the fact that multiple experts often yield multiple opinions. The goals of this work were (1) to develop and validate an expert system to assist the medical team deliver efficient, quality care to children with recurrent medulloblastoma, a common type of pediatric brain tumor, and (2) to determine if the expert system can be used as an educational tool. The results of our study indicate that residents enjoy learning by using XNEOr, the brain tumor expert system. XNEOr enabled residents to order appropriate ancillary tests for patients and to make fewer incorrect treatment decisions. The potential net effect of residents using XNEOr may be increased patient and family satisfaction and decreased probability of medical liability. At a time of important changes in our health care system, novel expert systems hold promise as tools to reduce medical costs, improve the quality of multi-expert medical care, and advance health care education.

INTRODUCTION

The management of brain tumors is complex because of the required involvement of specialists from multiple medical disciplines including neurosurgery, neurology, radiation oncology, hematology-oncology, neuropsychology, and rehabilitation medicine [1]. This complexity has lead some to claim that pediatric brain tumors cannot be approached algorithmically [2]. However, advances in computer and information technology can provide physicians and other allied health professionals with expert systems that transform complex clinical knowledge into efficient management and educational tools [3,4]. Medulloblastoma is one of the most common

brain tumors in the pediatric age group [5]. The tumor produces symptoms such as headache, nausea and vomiting, and gait imbalance. Magnetic resonance imaging (MRI) of the brain provides valuable information on the tumor's size and degree of involvement of the brain. Once the tumor is detected with MRI, the patient undergoes an operation to remove as much of the tumor as possible. Because of the propensity of medulloblastoma to grow back (recur) following surgery alone, the patient is then treated with radiotherapy and chemotherapy. The medical team meets to develop a proposed treatment plan that is established based on the risk that the tumor will recur and the risk that therapy will produce unacceptable side effects. The risk that a medulloblastoma will recur can be estimated by considering a variety of factors including tumor size, extent of brain involvement, degree of spread in the spinal fluid spaces, and extent of the surgical resection. Brain tumor referral centers including the one at the University of Florida hold multi-expert conferences and clinics to develop comprehensive treatment options for patients.

The multi-expert decision-making process in brain tumor referral centers is costly, time consuming, and complicated by the following factors: (1) experts are often inaccessible owing to conflicting scheduling, (2) junior members of the team are reluctant to propose management strategies because of the presence of more senior physicians, the so-called "upward ripple paranoia", (3) management decisions in patients with similar clinical risk factors are not consistent over time, and (4) multiple experts often yield multiple opinions. In addition, physicians in residency training are in need of educational tools that capture the decision-making skills of multiple experts.

The absence of a system to develop truly cohesive and consistent management strategies

for patients can reduce the quality of care and increase medical costs. Uncertainties about patient management can increase the number of unnecessary ancillary tests ordered by residents. Moreover, the risk of medical liability increases for physicians making less than optimal patient management decisions. We designed *XNEOr*, an expert system that corrects many inefficiencies in managing children with brain tumors.

Previous Work

During the past decade, medical expert systems have been developed for diagnosis (INTERNIST-1/CADUCEUS, NEUROLOGIST-1, NEUREX, ANGY, CENTAUR), diagnosis and therapy (MYCIN, CASNET/GLAUCOMA, EMERGE, IRIS, ARAMIS), and monitoring and therapy (BABY, ANNA, MED-1, ONCOCIN) [6-19]. Most of these expert systems were engineered from single medical domains such as neurology, oncology, and pediatrics.

We previously developed and tested a radiation oncology expert system (single medical domain), *XNEOn*, for managing patients with newly-diagnosed medulloblastoma [20]. We asked the following question: can *XNEOn* be designed to correctly select radiation treatment doses, fractions and volumes for patients with newly-diagnosed medulloblastoma? Knowledge was extracted from radiation oncologists and represented in decision rules in the expert system shell *Exsys Pro*. *XNEOn* was tested for accurate decision-making in 11 hypothetical clinical cases. *XNEOn* found the correct treatment plan in 9 cases (82%). In two cases, the rules had been constructed incorrectly in that they specified radiation treatment for all patients at diagnosis, including infants (which can produce untoward effects on the developing brain of the infant). Success with the modified version of *XNEOn* motivated the development of *XNEOr* for recurrent medulloblastoma, a significantly more complex clinical problem. We used an incremental approach to building *XNEOr* because there is considerably more uncertainty about the value of various combinations of surgery, radiotherapy and chemotherapy than for newly-diagnosed medulloblastoma. We modularized the knowledge representation to provide users of the new system with a good explanation facility and interface in managing patients.

System Development

XNEOr was developed by using several of the classical stages of software engineering including specification, conceptualization, formalization, prototyping, implementation, validation and verification, and modification. Knowledge acquisition and representation was intricate: firstly, several independent decision trees were designed for each treatment modality; secondly, the detailed knowledge extracted from each of the experts was coalesced and modeled into extensive flow charts, and integrated into 92 decision rules (production rule format) with 30 optimal treatment solutions. During the initial development stages, the clinical decision trees were modified frequently by the experts. The final design has two levels in the depth of the knowledge within the decision trees. The first level provides for the correct selection of the treatment modalities (surgery, radiotherapy, chemotherapy) and the second level enables the user to select a detailed radiation plan including radiation dose, fraction size, treatment schedule, and treatment volume. In addition, *XNEOr* is designed to provide an explanation to the user of why a particular treatment is selected. For example, if the user of *XNEOr* selects the treatment modality "radiotherapy" in a very young child, *XNEOr* will specify that children younger than three years of age should not be given radiotherapy because of the risks of injuring the developing nervous system.

The following clinical case illustrates an interaction with *XNEOr*. A two and one half year old girl was diagnosed with medulloblastoma and the tumor was surgically removed. She was then treated with chemotherapy without complications for 12 months. The chemotherapy was discontinued at that time since there was no evidence of residual tumor. At five years of age, she has developed headache, weakness and vomiting. MRI of the brain shows a 3 cm recurrent medulloblastoma in the cerebellum. MRI of the spine is normal. The spinal tap is positive for tumor cells. The 111 Indium CSF study is normal. The family is eager to carry on with any therapy recommended by the team of medical experts. In this example, all the *XNEOr* prompts and output are shown in plain type, the resident's input in **bold**, and comments about the interaction are shown in the parentheses:

- Enter the age of the patient in months:
60 months (the patient is 5 years old at the time of tumor recurrence)...
- Is the tumor symptomatic or asymptomatic ?
Symptomatic (headache, vomiting and weakness)...

• Was there any prior radiation ?
No (because of the child's young age at diagnosis, radiotherapy was not administered; she had received chemotherapy)...
• Is this recurrence localized or disseminated?
Disseminated (MRI of spine is negative but spinal tap shows the presence of tumor cells)...
• Is there gross spinal disease ?
No (MRI of spine is negative)...
• How was the previous chemotherapy tolerated?
Good tolerance...
• Is the 111 Indium CSF study normal?
Yes...
• Are there any socio-economic factors or other factors that preclude additional therapy?
No...

The output of the system is given as follows: Give radiation therapy (NOTE: Give cranio-spinal irradiation (CSI) with boost to any gross metastatic disease with standard dose comprising of CSI : 2500 to 3600 cGy, posterior fossa : 5500 cGy; No Neurosurgery (NOTE: Since the disease is disseminated, neurosurgery is not recommended); Consider intrathecal chemotherapy via an Ommaya Reservoir.

Validation and Verification

Ten hypothetical clinical cases of recurrent medulloblastoma were prepared by one of the co-authors (BLM) who is knowledgeable about this disease and its clinical manifestations. The hypothetical patients had a broad range of symptoms, physical examination findings and laboratory results so as to reflect the diversity of clinical manifestations of medulloblastoma. The same 10 cases were then executed on *XNEOr* and the experts determined that *XNEOr*'s treatment selections (levels I and II) were correct in the 10 cases.

Five of eight radiation oncology residents familiar with the workings of the multidisciplinary brain tumor group of experts at the University of Florida were randomly selected for participation in the study comparing their performance in managing the 10 cases with and without the aid of *XNEOr*. All five residents consented to participate. They were instructed to request as few or as many tests as necessary to prescribe a correct overall treatment plan (level I) and the correct radiation treatment parameters (level II), when appropriate. They were asked to be cost effective and to order only those ancillary tests required to prepare a treatment plan.

Each resident studied the 10 cases independently. In each case, the resident ordered tests to formulate a treatment plan. The experts had pre-determined what tests were required for correct treatment decisions. When an appropriate test was ordered by the resident, the results of the test were provided by the examiner. When an unnecessary test was ordered, the residents were told that the results were pending. The residents were unaware of whether the results of pending tests would be provided to them during the interaction. The residents were then asked whether the patient should have surgery, radiotherapy and chemotherapy. When radiotherapy was selected, the radiation oncology residents were asked to provide details on radiation dose, schedule, fraction size and volume. After specifying overall management and treatment decisions in all 10 cases, each resident then conducted an interactive consultation with *XNEOr* on the same 10 cases. In all, 50 independent trials were conducted by the five residents with 10 trials each. The radiation treatment decisions were reviewed by an expert radiation oncologist amongst the authorship (RM) and scored as (C) correct and agrees with *XNEOr*, (I) incorrect but still within acceptable standards of radiation oncology care, (D) dangerous or serious, and (L) potentially life-threatening. We then determined (1) if the correct treatment modalities (surgery, radiotherapy, chemotherapy) were selected, (2) if the correct radiation dose, schedule, fraction and volume were selected, (3) if the appropriate medical tests were ordered, and (4) how the residents rated their interactions with *XNEOr*.

RESULTS

Before using *XNEOr*, the residents collectively ordered a total of 46 unnecessary tests including computed tomograms of the head, complete bone scans, bone marrow aspirations, and single photon emission computed tomographies. The residents failed to order a total of 59 tests required for decision-making including lumbar punctures for analysis of the cerebrospinal fluid and MRI.

The residents correctly selected all three treatment modalities of surgery, radiotherapy and chemotherapy in $32 \pm 7\%$ (95% CI = 18-46%) of cases (Table 1). They selected the correct radiation dose, schedule, fraction and volume in $50 \pm 7\%$ (95% CI = 22-78%) of cases (Table 2); $28 \pm 4\%$ of the radiation oncology residents radiation treatment decisions were scored as dangerous or life-threatening by the radiation oncology expert.

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With *XNEOr*, the residents ordered the appropriate tests and selected the correct therapy in 100% of cases tested. Five of five residents said they would use *XNEOr* for learning and in their future clinical practice (Table 3). One of the five residents rated the explanation facility of *XNEOr* as fair and requested that literature citations be used to support underlying decision-rules. One of the five residents had considerable *a priori* experience with advanced user interfaces. This resident rated the user interface as "fair".

Table 1. Overall Treatment Decisions.

Subject No.	3 of 3	2 of 3	1 of 3
1	0.4	0.4	0.2
2	0.3	0.3	0.4
3	0.3	0.6	0.1
4	0.3	0.3	0.4
5	0.3	0.6	0.1
Mean	0.32	0.44	0.24
Sample SD	0.05	0.067	0.078
Binomial SD	0.07	0.07	0.06
95% CI	18,46	30,38	12,36
Std. error	3%	3%	3%

Table 2. Radiation Treatment Decisions.

Subject No.	C	I	D	L
1	0.6	0.2	0.1	0.1
2	0.4	0.4	0.2	0
3	0.4	0.1	0.5	0
4	0.4	0.2	0.4	0
5	0.7	0.2	0.1	0
Mean	0.5	0.22	0.26	0.02
Sample SD	0.06	0.049	0.08	0.02
Binomial SD	0.07	0.044	0.06	0.02
95% CI	22,78	12,32	10,42	0,6
Std. error	3.13%	2.20%	3.60%	1%

Table 3. Feedback on use of *XNEOr*.

Criteria	1	2	3	4	5
Use in Practice	yes	yes	yes	yes	yes
Explanations	ok	ok	ok	good	fair
User Interface	ok	ok	good	fair	good
Tutoring	good	good	good	ok	good

DISCUSSION

Diagnostic reasoning is used in many areas including debugging software programs, fault localization in electronic circuits, and automobile engine failure. Medical diagnostics uses abductive inferencing as a problem-solving

methodology. A diagnostician identifies one or more significant diseases that may cause a subset of symptoms by associating causal relationships. If a set of symptoms and clinical findings (manifestations) suggests increased intracranial pressure in a child (headache, vomiting, weakness), a physician identifies, through hypothesis generation, a set of diseases (differential diagnosis) that can account for the manifestations. Then, certain laboratory tests including an MRI of the head will be ordered to more clearly define the underlying problem. The results of this study suggest that, while complex, pediatric brain tumors can be approached algorithmically and their management can be modeled in rule-based expert systems.

Patients with medulloblastoma must have access to more than one medical expert to receive quality care. Medical decision-making in such patients is complex and time-consuming. We developed *XNEOr*, an intricate rule-based expert system that improves the efficiency of decision-making by residents in children with recurrent medulloblastoma. While the data presented on evaluation of *XNEOr* in five residents must be considered preliminary, the system may offer important cost-savings. *XNEOr* may potentially (1) reduce the time required by residents or primary care providers to interact with multiple experts, (2) reduce the number of inappropriate laboratory tests ordered, and (3) reduce the variability (and cost variance) in the assessment and treatment of patients. In building *XNEOr*, we captured the skills and heuristics of professionals in neurosurgery, radiation oncology, and hematology/oncology. Thus, *XNEOr* may be a valuable educational resource in other institutions and centers where residents are learning to evaluate and treat children with brain tumors.

XNEOr will need regular updating, validation and verification. We will research how changes in the medical management of medulloblastoma can be incorporated into *XNEOr* in a cost effective manner. We will need to determine if residents learn from*XNEOr* and if the system has limitations in handling an even broader range of clinical cases. Our experience in designing *XNEOr* would suggest that expert systems using production rules and an algorithmic approach can mimic complex decision-making involving multiple experts.

Future Research

Many current database applications in engineering, manufacturing, communications and medicine demand some reasoning in their processing activities. There is an explicit need to provide a database management system (DBMS) to store data and manage the XNEOn and XNEOr expert systems. However, such applications require more sophisticated control mechanisms than simple value matching. Conventional DBMS fail to meet the requirements of the brain tumor domain because they are passive in nature whereas our expert systems require database support to react to a variety of situations defined over the state of the system and specific events that demand immediate actions. Thus, Active Databases may therefore be required to provide support to our expert systems.

In conclusion, expert systems like XNEOr will undoubtedly benefit patients by enhancing the management of brain tumors. The potential net effect of XNEOr may be increased patient and family satisfaction, increased empowerement of health care professionals, and decreased probability of medical liability. At a time of important changes in our health care system, novel expert systems that confront the challenges of multi-expert decision-making hold promise as tools to reduce costs, improve the quality of care, and advance health care education.

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